

Summary Statement Title:

Prophylactic vaccination against human papillomavirus infection and disease in women: Evidence and implications for public health

Review Quality Rating: 9 (Strong)

Review on which this summary statement is based:

Rambout, L., Hopkins, L., Hutton, B., & Fergusson, D. (2007). **Prophylactic vaccination against human papillomavirus infection and disease in women: A systematic review of randomized controlled trials.** *Canadian Medical Association Journal*, 177(5), 469-479.

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This is a summary statement written to condense the work of the authors of this systematic review, referenced above. The intent of this summary is to provide an overview of the findings and implications of the full review. For more information on individual studies included in the review, please see the review itself.

Review content summary

The goal of this review was to combine the results of 6 randomized controlled trials (with a total of 40, 323 participants) assessing the impact of human papillomavirus (HPV) vaccines from 9 reports. To be included, trial vaccines had to contain coverage against at least 1 cancer-causing HPV strain (e.g. types 16 and 18). All of the vaccines administered contained coverage against HPV type 16. The primary outcome of interest was the frequency of high-grade cervical lesions. The secondary outcomes were persistent HPV infection, low-grade cervical lesions, external genital lesions, adverse events and death. Study participants were women, aged 15 to 25 years, primarily Caucasian descent, with some women of Hispanic, Asian and black descent. The majority of the women had no prior abnormal Pap test results, and all were seronegative for HPV strains 16 and/or 18. Studies took place primarily in North America, Latin America, Asia Pacific and Europe. All published and unpublished reports of randomized controlled trials were eligible for review, with no exclusion on the basis of language or year of publication. Comparators had to be either placebo or a “no HPV vaccination” group. The review determined that HPV vaccination is highly effective in preventing vaccine type-specific HPV infection and precancerous cervical disease, particularly among women aged 15–25 years with no history of abnormal Pap test results, and no more than 6 lifetime sexual partners. Moreover, the vaccination appears to be well tolerated and safe. Further research is needed to demonstrate efficacy in more representative populations of women, the possible implications of vaccinating against only 2 cancer-causing HPV strains, and the duration of vaccine efficacy.

Comments on this review’s methodology

This is a methodologically strong review. Five electronic databases were searched to 2007 and authors also consulted reference lists, Google Scholar, grey literature and contacted key informants. Two of the primary reviewers performed quality assessments independently using the scale previously validated by Jadad et al. Third-party consultation was used to resolve discrepancies between primary reviewers. All 6 studies were of high methodological quality (score of 5/5 on the Jadad scale). Heterogeneity was assessed using the I_2 statistic, and effect sizes are presented as Peto odds ratios with associated 95% confidence intervals. Pooled estimates and their confidence intervals were obtained using a fixed-effects model and presented in Figures 2-4.

Why this issue is of interest to public health

HPV is estimated to be one of the most common sexually transmitted infections (STIs) in Canada, affecting approximately 550 000 Canadians annually.^{1,2} It is estimated that as many as 75% of sexually active men and women will have at least one HPV infection in their lifetime.¹ Given that there is no cure for HPV and that it is the root cause of most cervical cancers, its prevention warrants attention. Current estimates indicate that each year 580 Canadian women die from cervical cancer, and cervical cancer is the third most frequent cancer in women aged 20-49 years.² The yearly overall cost of invasive disease and death in Canada from cervical cancer has been estimated at up to \$270,000,000.³ HPV types 16 and 18 cause approximately 70% of cervical cancers.¹ Despite Canada’s progressive Pap test screening initiatives, the disease is still a major problem because detection is both challenging and costly: screening is less accurate with early-stage cervical cancer, and symptoms are often only detected in later stages. In Canada four million Pap tests are done each year at an estimated cost of \$200,000,000.³ Canadian studies show that about 60% of cervical cancers occur in women who have not been screened in the previous three years.³ The vaccine approved for use in Canada, Gardasil™, protects against infection with two high-risk types of HPV (16 and 18) and two low-risk types (6 and 11). Vaccination may represent the best primary method of HPV prevention, as condoms have limited efficacy without consistent use, and abstinence is unacceptable to many.³

Evidence and implications

Evidence points are weighted or ranked according to strength (Y)

What's the evidence?	Implications for practice and policy:
<p>1. High-grade cervical lesions (5 studies)</p> <p>1.1. At 15-60 months post vaccination, participants who received the HPV vaccine were 48% less likely to develop high-grade cervical lesions than those not immunized. The true effect ranged from 57% to 37% less likely [OR 0.52, 95% CI 0.43 to 0.63 in the modified ITT meta-analysis (n=18096)].</p>	<p>1. High-grade cervical lesions</p> <p>1.1. Public health organizations should consider promoting complete, 3-dose, HPV vaccination among women aged 15 to 25 years who have not previously been infected with vaccine-type HPV strains</p>
<p>2. Any cervical lesions (5 studies)</p> <p>2.1. At 15-60 months post vaccination, participants who received the HPV vaccine were 64% less likely to develop any cervical lesions than those not vaccinated. The true effect ranged from 71% to 55% less likely [OR 0.36, 95% CI: 0.29 to 0.45 in the modified ITT meta-analysis (n=11267)].</p>	<p>2. Any cervical lesions</p> <p>2.1. Public health organizations should consider promoting complete, 3-dose, HPV vaccination among women aged 15 to 25 years who have not previously been infected with vaccine-type HPV strains.</p>
<p>3. Persistent Type 16 or 18 HPV Infection</p> <p>3.1. At 6 months post vaccination, participants who received the HPV vaccine were 77% less likely to develop persistent HPV infection. The true effect ranged from 82% to 73% less likely [OR 0.22, 95%CI 0.18 to 0.27 in the modified ITT meta-analysis (n=7081) (3 studies)].</p> <p>3.2. At 12 months post vaccination, participants who received the HPV vaccine were 74% less likely to develop persistent HPV infection. The true effect ranged from 84% to 59% less likely [OR 0.26, 95%CI 0.16 to 0.41 in the modified ITT meta-analysis (n=3861) (2 studies)].</p>	<p>3. Persistent HPV Infection</p> <p>3.1. Public health organizations should consider promoting, complete, 3-dose, HPV vaccination among women aged 15 to 25 years who have not previously been infected with vaccine-type HPV strains.</p>
<p>4. External genital disease (2 studies)</p> <p>4.1. At 15-60 months post vaccination, participants who received the HPV vaccine were 70% less likely to develop external genital diseases than those not immunized. The true effect ranged from 78% to 57% less likely [OR 0.30, 95% CI 0.22 to 0.43 in the modified ITT meta-analysis (n=2988)].</p>	<p>4. External genital disease</p> <p>4.1. Public health organizations should consider promoting complete 3-dose, HPV vaccination among women aged 15 to 25 years who have not previously been infected with vaccine-type HPV strains.</p>
<p>5. Adverse events and death (6 studies)</p> <p>5.1. At 15-60 months post vaccination, participants who received the HPV vaccine were no more or less likely to experience serious adverse events than those not vaccinated.</p> <p>5.2. At 15-60 months post vaccination, participants who received the HPV vaccine were no more or less likely to die than those who had not been vaccinated.</p>	<p>5. Adverse events and death</p> <p>5.1. Public health organizations should consider promoting complete, 3-dose, HPV vaccination among women aged 15 to 25 years who have not previously been infected with vaccine-type HPV strains.</p>
<p>6. Methodological issues with primary studies</p> <p>6.1. High drop-out rates</p> <p>6.2. Lack of outcomes related to specific HPV subtypes</p> <p>6.3. Lack of long term follow-up</p>	<p>6. Future research</p> <p>6.1. Rigorous program evaluation and high quality research studies should be conducted to determine the long term effectiveness of the HPV vaccine.</p>
<p>7. Cost Benefit or Cost-Effectiveness Information</p> <p>7.1. No cost related information was included in the review</p>	<p>7. Cost Benefit or Cost-Effectiveness Information</p> <p>7.1. Future research should assess cost benefit or cost-effectiveness of the interventions</p>
<p>General implications</p> <ul style="list-style-type: none"> • HPV vaccination can prevent type-specific HPV infection and precancerous cervical lesions in healthy young women (15–26 years of age) who receive all 3 doses of the vaccine and have not been previously infected with these strains. • The long-term effectiveness of HPV vaccines in reducing the incidence of and mortality associated with cervical cancer is not known. Rigorous program evaluations and high quality research studies should be conducted to determine the long term effectiveness and any long term adverse effects of the HPV vaccine. 	
<p>Legend: CI – Confidence Interval; OR – Odds Ratio; RR – Relative Risk <i>**please see the health-evidence.ca glossary of terms (found under 'How to Use This Site') for definitions</i></p>	

References used to outline this issue

1. Health Canada. (2007). *Diseases and conditions, HPV*. Retrieved from <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/diseases-maladies/hpv-vph-eng.php>
2. The Society of Obstetricians and Gynaecologists of Canada. (2008). *Spread the word not the disease: hpvinfo.ca*. Retrieved from <http://www.hpvinfo.ca/hpvinfo/home.aspx>
3. Society of Obstetricians and Gynaecologists of Canada, HPV Consensus Guidelines Committee. (2007). Canadian consensus guidelines on human papillomavirus. *Journal of Obstetrics and Gynaecology Canada*, 29(8). Retrieved from http://www.sogc.org/guidelines/documents/gui196CPG0708revised_000.pdf

Other quality reviews on this topic

- Black, M.E., Yamada, J., & Mann, V. (2002). A systematic literature review of the effectiveness of community-based strategies to increase cervical cancer screening. *Canadian Journal of Public Health*, 93(5), 386-393.
- Black, M., Yamada, J., Bakker, R., Brunton, G., Cava, M., Camiletti, Y., et al. (2000). Community-based strategies to promote cervical cancer screening. Hamilton, Ontario: Effective Public Health Practice Project.
- Forbes, C., Jepson, R., & Martin-Hirsch, P. (2002). Interventions targeted at women to encourage the uptake of cervical cancer screening. *Cochrane Database of Systematic Reviews*, 3, Art. No. CD002834
- Shepherd, J., Peersman, G., Weston, R., & Napuli I. (2000). Cervical cancer and sexual lifestyle: A systematic review of health education interventions targeted at women. *Health Education Research*, 15(6), 681-694

Related links

- Canadian Cancer Society http://www.cancer.ca/Quebec/Prevention/Infectious%20agents/Human%20papillomavirus%20HPV.aspx?sc_lang=en
- Public Health Agency of Canada. Sexual health and Sexually Transmitted Infections <http://www.phac-aspc.gc.ca/publicat/std-mts/index-eng.php>
- National Advisory Committee on Immunization <http://www.phac-aspc.gc.ca/naci-ccni/>
- SOGC. Spread the word not the disease (patient pamphlet) http://www.hpvinfo.ca/hpvinfo/pdf/Quick-Facts-General-Info_e.pdf

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Robeson, P., McRae, L., Boyko, J., Dobbins, M. (2010). Prophylactic vaccination against human papillomavirus infection and disease in women: Evidence and implications for public health. McMaster University. Hamilton: ON. Retrieved March 23, 2010, from *health-evidence.ca*: http://www.health-evidence.ca/documents/17728/Rambout_2007_Summary_Statement_-_English.pdf

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